The recent availability of atypical or unconventional neuroleptic medications such as risperidone (Risperidal), olanzepine (Zyprexa), and quetiapine (Seroquel) promises to increase the safety and effectiveness of treating older patients with either late-onset delusional disorders, or with behavioral complications of Alzheimer's disease and other dementias. Over 70% of patients with Alzheimer's disease develop behavioral problems such as delusions, agitation, and aggression that require psychotherapeutic medication. In the past, typical or conventional neuroleptics such as haloperidol or chloropromazine have been used but have important side effects, especially extrapyramidal motor signs and symptoms and tardive dyskinesia. The atypical neuroleptics are characterized by serotoninergic antagonism. Although they are different from each other the atypical neuroleptics are better tolerated than are conventional neoroleptics.

By the end of 1998, physicians should have a choice of four different cholinesterase inhibitors for the treatment of Alzheimer's disease. A substantial proportion of patients with Alzheimer's disease have improved cognition and improved activities of daily living with these medications. Unfortunately, although the drugs appear to improve symptoms, they do not seem to alter the course of the illness. There is new but uncontrolled evidence that cholinesterase inhibitors might also mitigate the emergence of some behavioral symptoms of the illness, including delusions, and may also be useful for patients with severe cognitive impairment.

Last year, the results of a randomized controlled trial indicated the potential efficacy of vitamin E and/or selegiline (Eldepryl) in altering the symptomatic course of Alzheimer's disease. Patients on either of the medications alone or in combination remained in the community and avoided nursing home placement about five to seven months longer than those on placebo. Although there was less deterioration of activities of daily living, there was no change in cognitive function, suggesting that it might be possible to change some elements of the illness without affecting the core cognitive clinical features.

Suggestions have been made that estrogen replacement therapy or anti-inflammatory therapy may delay the onset of Alzheimer's disease, because estrogen is neurotrophic to cholinergic neurons and inflammatory processes attend the progressive neurodegeneration. Although observational studies have supported this, there have yet to be adequate randomized clinical trials. Therefore, these approaches remain reasonable but unproven.

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The New Antipsychotic Compounds: Is a Clinical Choice Algorithm Possible?

MOST DRUG TRIALS for schizophrenics have used conventional antipsychotics in the control treatment-arm of the experiment and have tended to involve narrowly defined, homogeneous schizophrenia subject populations. The newer antipsychotic medications (including clozapine) all have lower extrapyramidal toxicity than their conventional counterparts. The clinical groups, therefore, that have sensitivity to neurotoxic side effects (i.e. first break subjects, children, older patients, non-schizophrenic psychotic conditions) should derive the greatest benefit from this characteristic, but few studies address these groups. It is therefore not possible to make direct comparisons of effectiveness or toxicity among the various newer medications, particularly for the more "normal" clinical population, but some conclusions can be drawn, and a few predictions made.

Among the available novel agents, clozapine and quetiapine possess the lowest extrapyramidal toxicity, followed closely by olanzapine and then risperidone. When extrapyramidal toxicity dominates the clinical picture, clozapine or quetiapine should be the first choice. Other toxicities associated with clozapine, (blood dyscrasias, seizures, sedation, cardiotoxicity, etc.), however, prevent its easy clinical use, even in cases of severe acute extrapyramidal toxicity.

The newer agents also differ from conventional compounds along endocrinologic lines. Clozapine and quetiapine do not elevate prolactin, and olanzapine generally induces only a mild, and usually transient, prolactin elevation. Risperidone, on the other hand, elevates prolactin at least as much or more than its conventional counterparts. In clinical circumstances where prolactin elevation is of clinical concern, as in young or adolescent females, or patients with clinical intolerance of hyper prolactinemia—amenorrhea, galactorrhea, gynecomastia, testicular atrophy, erectile incompetence—clozapine, quetiapine, or olanzapine should be used. Again however, because of the predominance of other toxicities with clozapine, olanzapine and quetiapine would be superior first choices. Other toxicities that are of clinical significance and do vary among this class include sedation, weight gain, and cardiovascular toxicity. Sedation is most severe with clozapine, and is generally the titration-limiting characteristic of this compound. Olanzapine has somewhat more sedative potential than either risperidone or quetiapine but substantially less than clozapine.

Weight gain should be anticipated with most of the new compounds. Forty percent of patients treated with atypical drugs will experience a greater than 10% weight gain. Measures to avoid weight gain are consistently

more effective than those employed to induce weight loss. Clozapine and olanzapine seem to stimulate more weight gain than risperidone and quetiapine. All of these compounds increase weight more than the high potency conventional medications.

Cardiovascular toxicity has become a clinical concern because sertindole has been noted to produce more QT prolongation than conventional medications. Although a precise rank ordering of the risk of inducing ventricular arrhythmias is not known at this time, clozapine seems to have somewhat more potential than any of the other three compounds. Orthostatic hypotension with reflex tachycardia is the other major cardiovascular toxicity induced by these drugs. Here again, clozapine is the most difficult agent, followed distantly by the other three compounds.

Quetiapine's toxic profile, while favorable in most respects, contains a theoretical increased risk of eye complications, since its use in certain animal models results in the development of cataracts. This animal toxicity prompted the manufacturer and the FDA to advise slip lamp examinations before, and during, quetiapine treatment. Because the time course to the development of clinically significant cataracts is very slow, it is not our clinical habit to obtain a slip lamp examination before treatment. Instead, we perform routine clinical ophthalmoscopy before treatment (as we do on all patients) and refer only chronically treated subjects for ophthamologic (or optometric) consultation. This way, only those subjects who are successfully treated with quetiapine, will have to undergo these more extensive, and expensive examinations.

On the other side of the clinical equation lies the question of relative efficacies among these compounds. For individuals who are resistant to conventional antipsychotic medication, such as haloperidol, clozapine is the most powerful medication. Clozapine also appears remarkably better than conventional medications in moderately refractory individuals. Among the other three compounds, only risperidone has shown therapeutic power superior to conventional medications in such groups. In treatment-responsive groups, both risperidone and olanzapine (but not quetiapine) appear superior to conventional drugs. A few studies have compared risperidone to olanzapine. These data suggest similar effectiveness, but, as mentioned above, somewhat different side effects.

In summary, these newer antipsychotic compounds, while clearly of lower extrapyramidal toxicity than their conventional counterparts, have other contraindications. The patients' specific clinical scenario must guide the clinician in choosing among these drugs. While clozapine is more toxic than the other three compounds, it is also the most powerful antipsychotic treatment available. Thus, when toxicity concerns predominate, clozapine will be a last resort, but when inefficacy is preeminent, clozapine should be tried earlier. Among the other three compounds, quetiapine in general is least toxic, but with the available data, also appears least effective. Choosing between risperidone and olanzapine is usually a choice between different toxicities, as they are equally effective. Olanzapine has more sedation, weight gain, and hepatotoxicity, and is more expensive, while risperidone has greater extrapyramidal and endocrinologic toxicity. Future studies should help delineate differences amongst the atypical drugs, allowing clinicians to better assign priority for use of the drugs in various clinical circumstances.

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